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SKB 14136

SPECIFICATION

Be it known that I, GREGORY GALLAGHER, JR.
residing at 1130 Hollow Road, Collegeville, Pennsylvania
19426, a citizen of the United States, have invented new
and useful 4-AMINOALKYL-2(3H)-INDOLONES, of which the
following is a full, clear and exact specification.

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4-AMINOALKYL-2(3H)-INDOLONES

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S U P

This invention relates to certain novel 4-aminoalkyl-2(3H)-indolones as well as to anti-hypertensive compositions and methods which use them.

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CLP 1/2 P

Background of the Invention

4-Aminoalkyl-7-hydroxy-2(3H)-indolones are described in U.S. Patent No. 4,314,944 to have a beneficial effect on abnormal conditions of the cardiovascular system. More specifically, such compounds are said to have a vasodilatation effect on the kidney which is similar to that of dopamine, thereby inducing anti-hypertensive activity due to a dopaminergic mechanism.

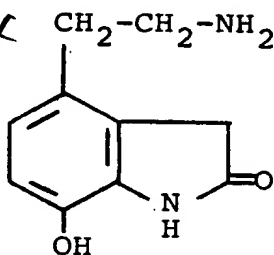
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The basic structure of the prior art compounds is similar to that of the well known cardiovascular agent they mimic, dopamine:

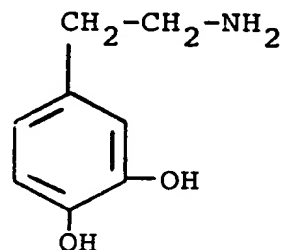
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U.S. Patent No. 4,314,944

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Dopamine

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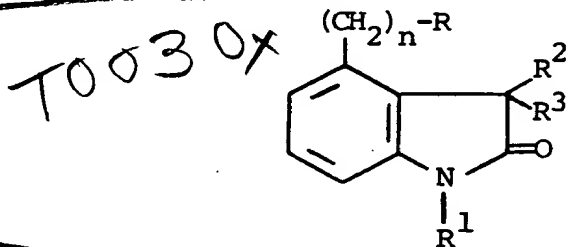
- 1 P One skilled in the structure function art will appreciate that the 7-hydroxy group of the compounds of the prior art is necessary for them to resemble the structure of dopamine. Without this key group, the
- 5 resulting compounds would not be expected to have cardiovascular activity.

CLP $\frac{1}{2}$ Description of the Invention

- The indolone compounds of this invention have beneficial cardiovascular activity despite the lack of the
- 10 supposedly essential 7-hydroxy group. In addition to not having a catechol or catechol-mimicking structure, these indolones may not be subject to tachyphylaxis and are better absorbed orally when compared with the prior art compounds based on preliminary pharmacological tests with
- 15 the preferred species of this invention.

P The compounds are illustrated by the following structural formula:

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PS 25 in which:

- P R is amino, lower alkylamino, di-lower alkylamino, allylamino, diallylamino, N-lower alkyl-N-allylamino, benzylamino, dibenzylamino, phenethylamino, diphenethylamino, 4-hydroxyphenethylamino or di-(4-hydroxyphenethylamino);
- 30

P R^1 , R^2 or R^3 are, each, hydrogen or lower alkyl; and

P n is 1-3.

- L A subgeneric group of this invention comprises
- 35 the compounds of formula I in which:

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1 ^P R is amino, di-n-propylamino, n-propyl-n-butyl-
amino or 4-hydroxyphenethylamino;

^P R¹, R² or R³ are hydrogen; and

5 ^L (CH₂)_n is ethylene (-CH₂-CH₂-).

^L A preferred species of this invention is
4-(2-di-n-propylaminoethyl)-2(3H)-indolone or one of its
pharmaceutically acceptable, acid addition salts.

27 28 The term "lower alkyl" used herein and in the
claims is meant, for convenience, to include branched and
10 straight chain groups of from 1-6 carbons, preferably n-
propyl, for each alkyl in R and from 1-4 carbons,
preferably methyl, for each of R¹, R² and R³. R¹,
R² and R³ are preferably, for ease of preparation, all
the same.

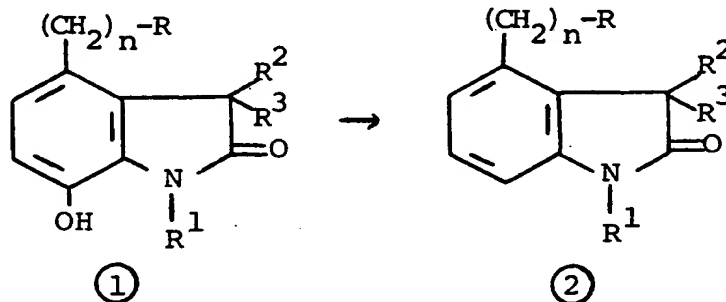
15 The pharmaceutically acceptable acid addition
salts having the utility of the free bases of formula I
are part of this invention. These are prepared by methods
well known to the art and are formed with both inorganic
or organic acids, for example: maleic, fumaric, benzoic,
20 ascorbic, pamoic, succinic, bismethylenesalicylic, methane
sulfonic, ethane disulfonic, acetic, oxalic, propionic,
tartaric, salicylic, citric, gluconic, aspartic,
stearic, palmitic, itaconic, glycolic, p-aminobenzoic,
glutamic, benzenesulfonic, hydrochloric, hydrobromic,
25 sulfuric, cyclohexylsulfamic, phosphoric and nitric
acids. The hydrohalic and, especially, methane sulfonic
acid salts are conveniently used.

^P The compounds of this invention are prepared by
the following reaction sequences:

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Scheme A

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Scheme B

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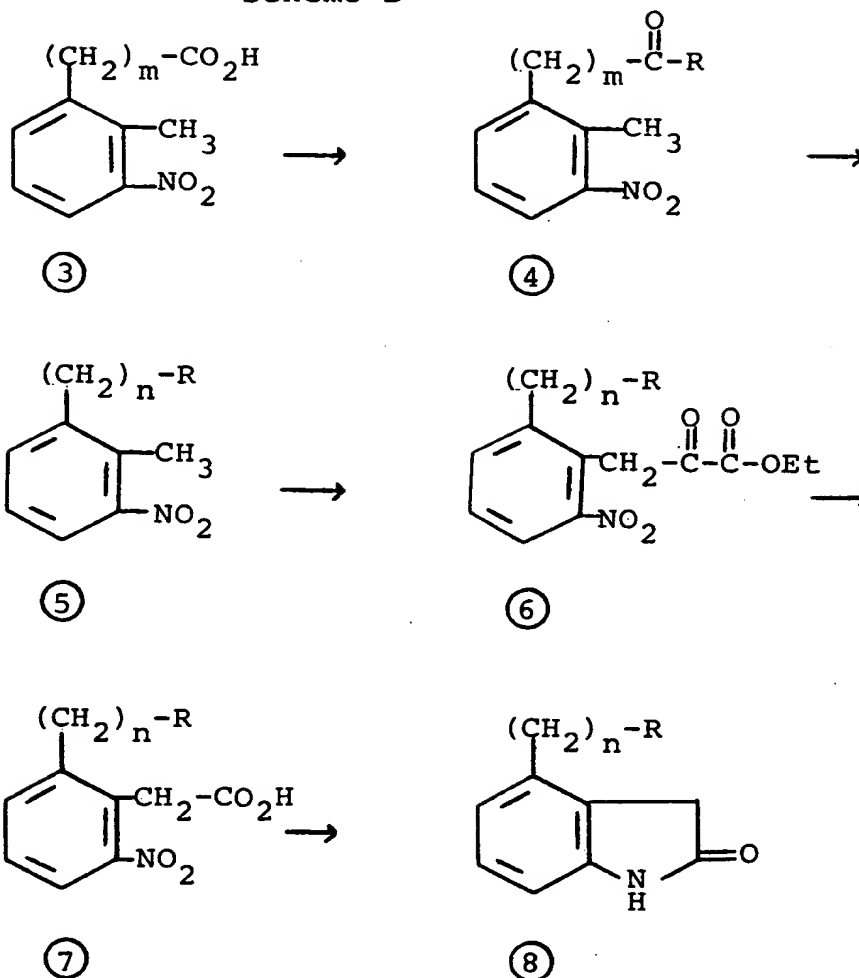
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In the reaction sequences of Schemes A and B above, n , R , R^1 , R^2 and R^3 are as described for

formula I; m is $n-1$. In some cases, such as where R is a primary or secondary amino, a protective group may be present, as described in more detail below.

In addition to the reaction sequences noted above, the compounds of this invention are prepared by the reactions which are described in U.S. Patent No. 4,314,944, using, of course, known deshydroxy or desmethoxy starting materials. In preparing the present 7-unsubstituted indolones by this route, the ring closure to form the

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1 isatin ring at column 2 of that patent can proceed to give
two isomeric products which must then be separated to yield
the indolones of this invention.

5 In Scheme A, the corresponding 7-hydroxy indolone
starting material (1) is de-hydroxylated by reacting it
with at least a stoichiometric quantity of a reactive
5-halo-1-phenyl-1H-tetrazole in the presence of an acid
binding agent, such as an alkali metal carbonate, in a
10 suitable inert solvent, such as aqueous acetone,
dimethylformamide or dimethylacetamide. The reaction is
carried out at room temperature until substantially
complete. From one to two days may be used. If desired,
the reaction may be carried out in shorter time by
20 operating at a higher temperature, for example, up to 75°.

15 The resulting new intermediate, a 4-(aminoalkyl)⊖
7-(1-phenyl-1H-tetrazol-5-yloxy)-2(3H)-indolone, is
subjected to hydrogenation to split the tetrazole-oxy-
indolone link. Conveniently, catalytic hydrogenation, for
example using a noble metal catalyst at moderate pressures
20 of hydrogen and some heat, such as palladium-on-charcoal
26 at 50° for 20 hours under 55 p.s.i., is used.

When R is a reactive amino, the starting material
(1) is used in the form of an acid addition salt or an
otherwise amino protected derivative. If a hydrogenation
25 labile protective group is present on compound 1, it is
also split during the reduction.

43 The reactions of Sequence B involve the insertion
of the aminoalkyl side chain into the phenyl ring (1→7)
30 followed by ring closure of the o-carboxymethyl-m-nitro
intermediate (7). The ring closure is carried out by
reduction of the intermediate, for example, using
catalytic hydrogenation over a noble metal, preferably
palladium, catalyst in a suitable solvent, for example, a
lower alcohol, dilute hydrochloric acid or glacial acetic
35 acid, at moderate pressures of hydrogen and at a tempera-
20 ture chosen from the range of room temperature to 60°.

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1 The reaction proceeds quickly to completion. The nitro
group of compound 7 is reduced first, followed by ring
closure.



5 As noted above, this reaction sequence is
adaptable to prepare the compounds having a reactive
aminoalkyl side chain by protecting an amine or another
reactive group with a standard protecting means such as
forming a maleimide, tert. boc or phthalimide derivative,
which is removed, by standard reactions, after ring
10 closure. The phthalimido protective group, for example,
is split using reaction with hydrazine hydrate. A
benzyloxy is split by using catalytic hydrogenation; a
tert.-boc, using mild acid.

15 The alkylated products of this invention are,
alternatively, or, in certain instances, preferentially
prepared by alkylation of the parent amino compounds of
formula I in which R is amino or a secondary amino. For
example, the N-alkylated products, formula I when R is a
secondary or tertiary amino, are conveniently prepared by
20 reductive alkylation using, for example, the aldehyde in
one or two molar equivalent quantities under reduction
conditions, such as under catalytic hydrogenation
conditions over a palladium or platinum catalyst or such
as using formaldehyde-formic acid when R is dimethylamino.


25 N-Alkylation, such as using an allyl or benzyl
halide in the presence of an acid binding agent, can be
used under standard mild conditions. Protecting the amido
hydrogen in the ring is also used during alkylation if
necessary as known to the art. Alkyl substituents at the
30 1 or 3-positions of the indolone ring are introduced by
forming the lithio derivatives at the ring position, such
as using butyl lithium, followed by reaction with a lower
alkyl halide, especially an alkyl iodide. This process is
similar to that reported by A. S. Kende et al., Syn.
35 Commun. 12 1 (1982).

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1 The compounds of this invention have utility, as
specific dopamine agonists, in the treatment of disorders
of the cardiovascular system, especially to treat hyper-
tension, to treat angina pectoris, to treat the symptoms
5 of congestive heart failure or to improve kidney function.

More specifically, the compounds of this
invention, especially 4-(2-di-n-propylaminoethyl)-2(3H)-indolone hydrochloride, have proved to be selective
peripheral D₂-agonists. For a discussion of various
10 agonist/antagonist activities in the dopaminergic system,
one should refer to J. M. Rooyen, et al., S. Afr. Med. J.
59 329 (1981). or I. Cavero et al., Life Sciences, 31 939,
1059 (1982). Otherwise speaking, the main focus of action
is at the presynaptic α -dopaminergic receptors which may
also be called "D₂-receptors." Activation of the D₂-
receptors on the sympathetic nerve terminals inhibits the
release of noradrenaline, thereby, promoting vasodilation,
among other beneficial cardiovascular actions.

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9 8 20 In the perfused rabbit ear artery test [J. P.
Hieble et al., Arch. Pharmacol., 309 217 (1979)], 4-(2-
di-n-propylaminoethyl)-2(3H)-indolone hydrochloride had an
EC₅₀ of 72nM. It was active in vivo in the dog in both
the cardiovascular nerve and perfused hind limb
preparations and did not cause tachyphylaxis in the latter
25 preparation as did its 7-hydroxy congener of the prior art.
Intravenous infusion of this species of this invention in
the DOCA-salt hypertensive and spontaneously hypertensive
rats reduced blood pressure and heart rate. A similar but
weaker effect on blood pressure and heart rate was
30 observed with the lead compound in the renal hypertensive
rat and in the normotensive rat tests. In conscious DOCA
salt hypertensive rats, oral doses of 10 mg/kg of the di-
n-propylaminoethyl compound demonstrated an anti-hyperten-
sive effect. This species seems more readily absorbed from
35 the gastrointestinal tract than is its 7-hydroxy congener.

The pharmaceutical compositions of this invention



1 which have pharmacodynamic activity within the
cardiovascular system, for example renal vasodilatation,
correcting hemodynamic imbalance, anti-anginal activity,
5 hypotensive activity and bradycardia, are prepared in
conventional dosage unit forms by incorporating a compound
of formula I, or a pharmaceutically acceptable acid
addition salt thereof, into a nontoxic pharmaceutical
carrier according to accepted pharmacy procedures in a
10 nontoxic quantity sufficient to produce the desired
pharmacodynamic activity in a subject, animal or human.
Preferably, the compositions will contain the active
ingredient in an active but nontoxic quantity selected
from the range of about 50 mg to about 500 mg, preferably
15 about 75-250 mg, of active ingredient, as the base, per
dosage unit. This quantity depends on the relative
potency of the base compound compared with that of the
prototypal species, 4-(2-di-n-propylamino-ethyl)-2(3H)-
indolone, as well as on the specific biological activity
20 desired, the route of administration, that is, whether
oral or parenteral, and the condition and size of the
patient.

The pharmaceutical carrier employed for the
dosage units is, for example, either a solid or liquid.
25 Exemplary of solid carriers are lactose, terra alba,
sucrose, talc, gelatin, agar, pectin, acacia, magnesium
stearate or stearic acid. Exemplary of liquid carriers
are isotonic saline for parenteral use or syrup, peanut
oil, olive oil or water for soft gelatin capsules.
30 Similarly, the carrier or diluent may include any time
delay material well known to the art, such as glyceryl
monostearate or glyceryl distearate alone or admixed with
a wax. Such sustained release products as well as pro-
drug derivatives which may be gradually metabolized to the
35 active parent can be employed to prolong the unique
biological activity of the compounds of this invention or
to attack receptors at a specific location.

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1 A wide variety of pharmaceutical forms can be
employed. Thus, if a solid carrier for oral or rectal
administration is used, the mixed preparation can be
tableted, placed in a hard gelatin capsule in powder or
5 sustained release pellet form, in a suppository or in the
form of a troche or lozenge. The amount of solid carrier
will vary widely but, preferably, will be from about 25 mg
to about 1 g. If a liquid carrier is used, the preparation
will be in the form of a syrup, emulsion, soft gelatin
10 capsule, sterile injectable liquid such as an ampul or an
aqueous or nonaqueous liquid suspension for oral
administration.

 The method of this invention for producing D₂^Q
agonist activity manifests itself by inducing renal
15 vasodilatation, anti-anginal, anti-hypertensive and
bradycardic activity. It comprises administering orally,
rectally or parenterally to a subject in need of such
activity a compound of formula I or a pharmaceutically
acceptable acid addition salt thereof, usually combined
20 with a pharmaceutical carrier, in a nontoxic amount
sufficient to produce said activity. The route of
administration may be any route which effectively
transports the active compound to the cardiovascular
system receptors which are to be selectively stimulated.
25 Such routes include oral, rectal or parenteral
administration, the oral route being preferred. The
parenteral administration may be subcutaneous or,
preferably, intravenous for critical use.

 Advantageously, doses selected from the dosage
30 unit ranges given above will be administered several
times, such as from one to five times, a day. The daily
dosage regimen is selected from the range of about 50 mg
to about 1.0 g, preferably 200^N 750 mg for oral administra-
tion and 50^N 500 mg for parenteral administration. When
35 the method described above is carried out, D₂-agonist
activity is produced.

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1 For an average size human using 4-(2-di-n-propyl-
aminoethyl)-2(3H)-indolone hydrochloride as an active
ingredient, a typical dose to show anti-hypertensive
activity would be selected from the range of from about
5 100-250 mg of base equivalent for each dosage unit which
is adapted for oral administration and which is administer-
ed orally from 1-4 times daily.

DE P The following examples are designed solely to
illustrate the preparation and use of the compounds of
10 this invention. The temperatures are Centigrade. Other
variations of these examples will be obvious to those
skilled in the art.

CL EXAMPLE 1

P A mixture of 3.44 g (9.63 mmoles) of 4-(2-di-n-
15 propylaminoethyl)-7-hydroxy-2(3H)-indolone hydrobromide
(U.S. Patent No. 4,314,944), 22 cc of dimethylformamide,
1.79 g (9.91 mmoles) of 5-chloro-1-phenyl-1H-tetrazole,
220 cc of acetone, 10 cc of water and 2.90 g (21 mmoles)
of anhydrous potassium carbonate was refluxed for about 3
20 hours at which time thin layer chromatographic analysis
(silica gel GF, 75-23-2 ethyl acetate-methanol-conc.
ammonium hydroxide) indicated that the reaction was
complete.

After cooling the reaction mixture in an
25 ice-bath, the inorganic salts were removed by filtration
and washed with acetone. The combined filtrates were
concentrated in vacuo. The residual syrup was diluted
with saturated brine and extracted with three portions of
diethyl ether. The gathered extracts were dried over
30 anhydrous magnesium sulfate, clarified with charcoal and
treated with ethereal hydrogen chloride until precipita-
tion was complete. The solid was slurried in diethyl
ether and decanted several times, filtered and air-dried
to give 3.8 g (86%) of tan 4-(2-di-n-propylaminoethyl)-7-
35 (1-phenyl-1H-tetrazol-5-yloxy)-2(3H)-indolone hydrochlo-
ride. Recrystallization from 200 cc of hot acetonitrile

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20 1 gave 2.6 g (59%) of microcrystalline product, m.p. 245-6°. Evaporation of the mother liquor and recrystallization of the residue from 25 cc of hot acetonitrile gave an additional 400 mg of product, m.p. 244-5°.

5 A mixture of 2.64 g (5.78 mmoles) of the phenyl tetrazole ether, 200 cc of glacial acetic acid and 1.49 g of 10% palladium-on-carbon was hydrogenated in a Parr apparatus at 50 p.s.i. for 20 hours at 50°. The warm reaction mixture was filtered through glass fiber filterpaper and the catalyst washed thoroughly with hot glacial acetic acid. The filtrate was concentrated in vacuo, the pale yellow waxy residue distributed in water and ethyl acetate. After acidification of the aqueous phase with 3N hydrochloric acid, the organic phase was separated and extracted once with 1N hydrochloric acid. The combined aqueous phases were adjusted to pH 8.5 with aqueous 10% sodium hydroxide and extracted with a mixture of ethyl acetate and diethyl ether. The combined organic extract was back-washed once with saturated brine, dried over anhydrous magnesium sulfate, clarified with charcoal, treated with ethereal hydrogen chloride and evaporated to dryness in vacuo to give 1.64 g (96%) of pale yellow crystalline solid; 4-(2-di-n-propylaminoethyl)-2(3H)-indolone hydrochloride. Recrystallization from 260 cc of hot acetonitrile which was concentrated to about 50 cc gave 1.26 g (74%) of pale yellow microcrystalline powder, m.p. 240-242°.

20 The hydrochloride salt (500 mg) is shaken in the presence of ether/5% sodium carbonate solution. The ether layer is separated, dried and evaporated to give the free base which is used to prepare other salt forms such as the methanesulfonate, ethanedisulfonate, sulfate or sulfamate by reacting aliquots of the base in ether with an excess of each acid.

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CL
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EXAMPLE 2

1 A mixture of 22.0 g (0.105 mole) of 2-methyl-3-nitrophenylacetic acid (V. Askam et al., J. Chem. Soc. (C) 1969 1935) and 25 cc of thionyl chloride was slowly heated
20 5 to 75° and the copious evolution of gasses allowed to moderate. The temperature was raised and the solution was refluxed for 1 hour. The reaction was concentrated in vacuo. The residual straw-colored syrup was chased several
20 10 times with dry toluene, diluted with 100 cc of dry toluene and added to a cool (10°) mixture of 13 g of sodium carbonate in 150 cc of water and 150 cc of toluene containing 14.5 cc (10.6 g, 0.12 mole) of di-n-propylamine with very slow stirring. After 30 minutes, the ice-bath was removed. Stirring was continued for one hour. An
15 additional 0.5 g of solid sodium carbonate was added to the reaction. After 15 minutes, the organic phase was separated, washed with 5% aqueous sodium carbonate followed by 2N hydrochloric acid and, finally, water. The organic solution was dried over magnesium sulfate,
20 concentrated in vacuo and pumped free of solvent to give 29.5 g of 2-methyl-3-nitrophenyl-N,N-di-n-propyl acetamide as a straw-colored syrup.

The total syrup (105 mmoles) was taken up in 250 cc of anhydrous tetrahydrofuran and treated with 160 cc of
25 1.0 M borane in tetrahydrofuran at room temperature for 1 hour. The reaction was refluxed for 2 hours, then cooled. Excess reagent was destroyed by the cautious addition of dry methanol. This solution was concentrated in vacuo. The residual syrup was treated with 40 cc of 6N

30 hydrochloric acid for 1 hour on the steam-bath, cooled, basified with 40% sodium hydroxide and extracted with 3 portions of ether. The combined organic phase was washed once with brine, concentrated in vacuo and distilled in a
20 Kugelrohr apparatus at 115°/118°/0.1 mm Hg to give 21.6 g
35 of a mobile yellow oil; 2-methyl-3-nitrophenylethyl-N,N-di-n-propyl amine.

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1 To a solution of 2.38 g (0.103 gram atoms) of
sodium metal in 52 cc of absolute ethanol at room tempera-
ture was added 18.51 g (0.07 mole) of the nitro compound
5 in one portion, with stirring, followed by 15.42 g (0.103
mole) of diethyl oxalate. The reaction was refluxed under
nitrogen for about 20 minutes, cooled, quenched on 700 cc
of ice-water and acidified with 3N hydrochloric acid.
This aqueous solution was washed with a small volume of
ether, basified to pH 8.5 with solid sodium carbonate and
10 extracted with 3 portions of ether. The combined ether
extract was washed with saturated brine, dried over
anhydrous magnesium sulfate, clarified with charcoal and
concentrated in vacuo. The residue was triturated with
cold petroleum ether, filtered and air-dried to give 6.0 g
15 of ethyl 6-(2-di-n-propylaminoethyl)-2-nitrophenyl-
pyruvate as a yellow powder. The triturate was
concentrated in vacuo and distilled to give 7.3 g of
recovered starting material which was recycled. In the
same manner, a total of three recycles provided 11.0 g of
20 ethyl-6-(2-di-n-propylaminoethyl)-2-nitrophenyl-
pyruvate.

20 A cold (10°) solution of 10.24 g (28.1 mmoles) of
the pyruvate in 196 cc of 2% sodium hydroxide was treated
with 5.0 cc of 30% hydrogen peroxide dropwise over several
25 minutes. The cooling bath was removed and stirring was
continued for 1.5 hours during which time the reaction
became much lighter in color. A small amount of insoluble
material was removed by filtration. The pH was adjusted
to 1.5 by the cautious addition (foaming) of about 12 cc
30 of conc. hydrochloric acid. This solution was concentrat-
20 ed in vacuo at 45°, reconstituted with water and
evaporated twice more. The residue was slurried in a
minimum volume of dilute hydrochloric acid, filtered and
air-dried to give 6.40 g of 2-nitro-6(2-di-n-propylamino-
35 ethyl)-phenyl acetic acid hydrochloride as a white powder.

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1 A mixture of 5.83 g (16.9 mmoles) of 2-nitro-6-
(2-di-n-propylaminoethyl)-phenyl acetic acid hydrochloride
and 0.6 g of 5% palladium-on-carbon in 250 cc of ethanol
was hydrogenated at 50 p.s.i. over 5.5 hours. The
5 catalyst was filtered, washed with ethanol, and the
filtrate evaporated to dryness in vacuo. The white
residue was crystallized from 550 cc of hot acetonitrile
to give 3.89 g of 4-(2-di-n-propylaminoethyl)-2(3H)indolone
hydrochloride, mp 240¹/_N2°.

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10 Anal. Calcd. for C₁₆H₂₄N₂O HCl: C, 64.74;
H, 8.49; N, 9.44. Found: C, 64.82; H, 8.26; N, 9.28.

P CL EXAMPLE 3

15 A mixture of 2.73 g (10.0 mmoles) of 4-(2-amino-
ethyl)-7-hydroxy-2(3H)-indolone hydrobromide (U.S. Patent
No. 4,314,944), 200 cc of dimethylformamide, 1.86 g (10.3
mmoles) of 5-chloro-1-phenyl-1H-tetrazole, 10 cc of water
and 2.9 g (21 mmoles) of anhydrous potassium carbonate is
stirred at room temperature for 2 days or until thin layer
analysis indicates that no starting material remains. The
20 reaction is filtered and the filtrate is acidified with
dil. hydrochloric acid, concentrated in vacuo and the
residue triturated with abs. ethanol. The triturate is
clarified with charcoal and evaporated to dryness in
vacuo. The hydrochloride salt of 4-(2-aminoethyl)-7-
25 (1-phenyl-1H-tetrazol-5-yloxy)-2(3H)-indolone is
hydrogenated directly in 200 cc of glacial acetic acid
using 50% by substrate weight of 10% palladium-on-carbon
20 at 50 p.s.i. for 20 hours at 50°. The warm reaction
mixture is filtered. The catalyst is washed thoroughly
30 with hot acetic acid. After the filtrate is concentrated
in vacuo, the residue is stripped several times from
dilute hydrochloric acid and crystallized from ethanol to
give 4-(2-aminoethyl)-2(3H)-indolone hydrochloride.

P CL EXAMPLE 4

35 A mixture of 0.5 g of 4-(2-aminoethyl)-2(3H)-
indolone hydrochloride, prepared as in Example 3, 2.2 g of

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1 isobutyraldehyde, 0.3 g of 5% palladium-on-charcoal and 75
ml of glacial acetic acid is hydrogenated at 55 p.s.i. of
hydrogen for 5 hours. The catalyst is separated by
5 filtration and washed with acetic acid. The combined
mother liquor-washings is evaporated in vacuo to give a
residue which is taken up in cold methanol and treated
with methanolic hydrogen bromide to give, upon
concentration and cooling; 4-(2-di-isobutylaminoethyl)-
10 2(3H)-indolone hydrobromide.

CL EXAMPLE 5

1 A mixture of 0.9 g of 4-(2-aminoethyl)-2(3H)-
indolone, 0.23 g of 4-benzyloxyphenylacetaldehyde, 0.25 g
of 10% palladium-on-charcoal and 100 ml of ethanol is
15 hydrogenated at 50 p.s.i. at 50° until the uptake of
hydrogen is complete. After filtration, the mother
liquors are evaporated to give 4-[2(4-hydroxyphenethyl-
amino)-ethyl]-2(3H)-indolone as the residue. This base in
alcohol is treated with an excess of methylsulfonic acid
20 to give the methylsulfonate salt.

Repeating this reaction with 4-n-propylamino-
ethyl-7-hydroxy-2(3H)-indolone and butyraldehyde gives 4-
n-butyl-n-propylamino-ethyl-7-hydroxy-2(3H)-indolone hydro-
chloride.

CL EXAMPLE 6

25 Substituting 2.2 g of 4-(3-dimethylaminopropyl)-
7-hydroxy-2(3H)-indolone hydrobromide (U.S. Patent No.
4,314,944) for 4-(2-di-n-propylaminoethyl)-7-hydroxy-
2(3H)-indolone hydrobromide in Example 1 gives 4-(3-di-
30 methylaminopropyl)-7-(1-phenyl-1H-tetrazol-5-yloxy)-2(3H)-
indolone hydrochloride and, then, 4-(3-dimethylamino-
propyl)-2(3H)-indolone base as well as the ethanedisul-
fonate salt as described above.

Substituting 4-n-propylaminoethyl-7-hydroxy-
2(3H)-indolone hydrobromide (U.S. Patent No. 4,314,944)
35 gives 4-n-propylaminoethyl-2-(3H)-indolone hydrochloride.

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1 Substituting 4-dimethylaminopropyl-7-hydroxy-
2(3H)-indolone hydrobromide (U.S. Patent No. 4,314,944)
gives 4-dimethylaminopropyl-2(3H)-indolone hydrochloride.

EXAMPLE 7

5 4-Aminoethyl-2(3H)-indolone (10 g) is reacted
with two mole equivalents of allyl bromide and 4
equivalents of triethylamine in acetonitrile with mild
heat for several hours. The reaction mixture is
evaporated. The residue is suspended in water. The
10 mixture is extracted with ethyl acetate. The extracts are
washed, dried and evaporated to give 4-di-allylamino-
ethyl-2(3H)-indolone. This material (1 g) is dissolved in
ether-ethanol and treated with methane sulfonic acid to
give the methane sulfonate salt. Using benzyl bromide
15 gives 4-dibenzylaminoethyl-2(3H)-indolone.

EXAMPLE 8

 Anhydrous tetrahydrofuran (10 cc) at 20° under
nitrogen was treated with 2.0 cc (4.8 mm) of 2.4 M ²⁰n-butyl
lithium in hexane followed by 0.49 g (1.5 mm) of 4-di-n-
20 propylaminoethyl-7-methoxy-2(3H)-indolone hydrochloride
and 0.349 g (3 mm) of N,N,N',N'-tetramethylethylene
diamine. Gas evolution and dissolution of the salt was
observed.

 The reaction mixture was cooled in a dry
25 ice-propanol bath and treated with 1.5 mm of iodomethane
in one portion. After stirring in the cold for 10 minutes,
the bath was removed and stirring continued for 2 hours.
The mixture was quenched in 20 cc of saturated ammonium
chloride solution, diluted with ethyl ether. The organic
30 layer was separated. The remaining material was again
extracted twice. The combined dried extracts were
concentrated in vacuo, stripped from ethyl ether and
carbon tetrachloride.

 Analysis of the solid demonstrated a mixture of
35 10% starting material and a 50-50 mixture of di- and mono

1 3-methylated product. The mixture was realkylated to give
169 mg of 3,3-dimethyl-4-di-n-propylaminoethyl-7-methoxy-
2(3H)-indolone.

5 This material is hydrolyzed as described in U.S.
Patent No. 4,314,944, Example 4 then, dehydroxylated in
the form of the crude product as described above to give
3,3-dimethyl-4-di-n-propylaminoethyl-2(3H)-indolone
hydrochloride.

10 The Kende process was repeated using the same
quantities but using 0.61 cc (9.8 mm) of methyl iodide at
-70°. The mixture was allowed to warm to -25° and held
there for 1 hour followed by 3 hours at room temperature.
After working up as described, 4-di-n-propylaminoethyl-7-
15 methoxy-3-methyl-2(3H)-indolone was recovered. This is
treated with boron tribromide and, then, 5-chloro-1-
phenyl-1H-tetrazole to give 4-di-n-propylaminoethyl-3-
methyl-2(3H)-indolone hydrochloride.

EXAMPLE 9

20 4-(2-di-n-Propylaminoethyl)-2(3H)-indolone hydro-
chloride (125 mg) is mixed with 200 mg of lactose and 2 mg
of magnesium stearate, filled into a hard gelatin capsule
and administered to a hypertensive patient from 1¹/₃ times
daily.

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